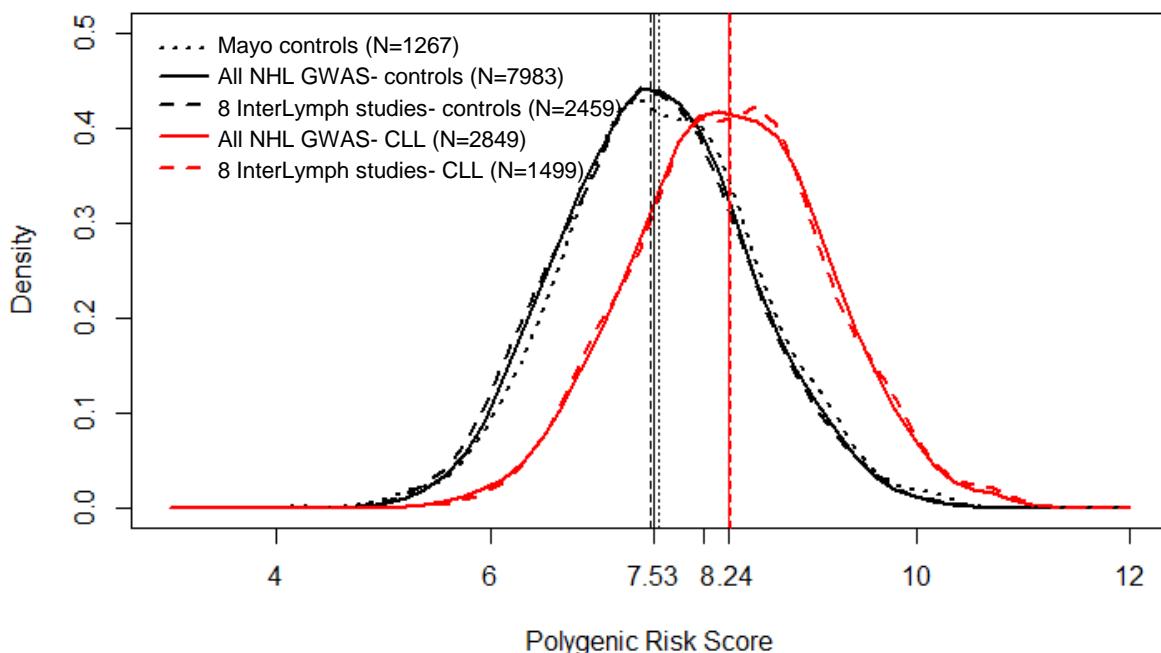


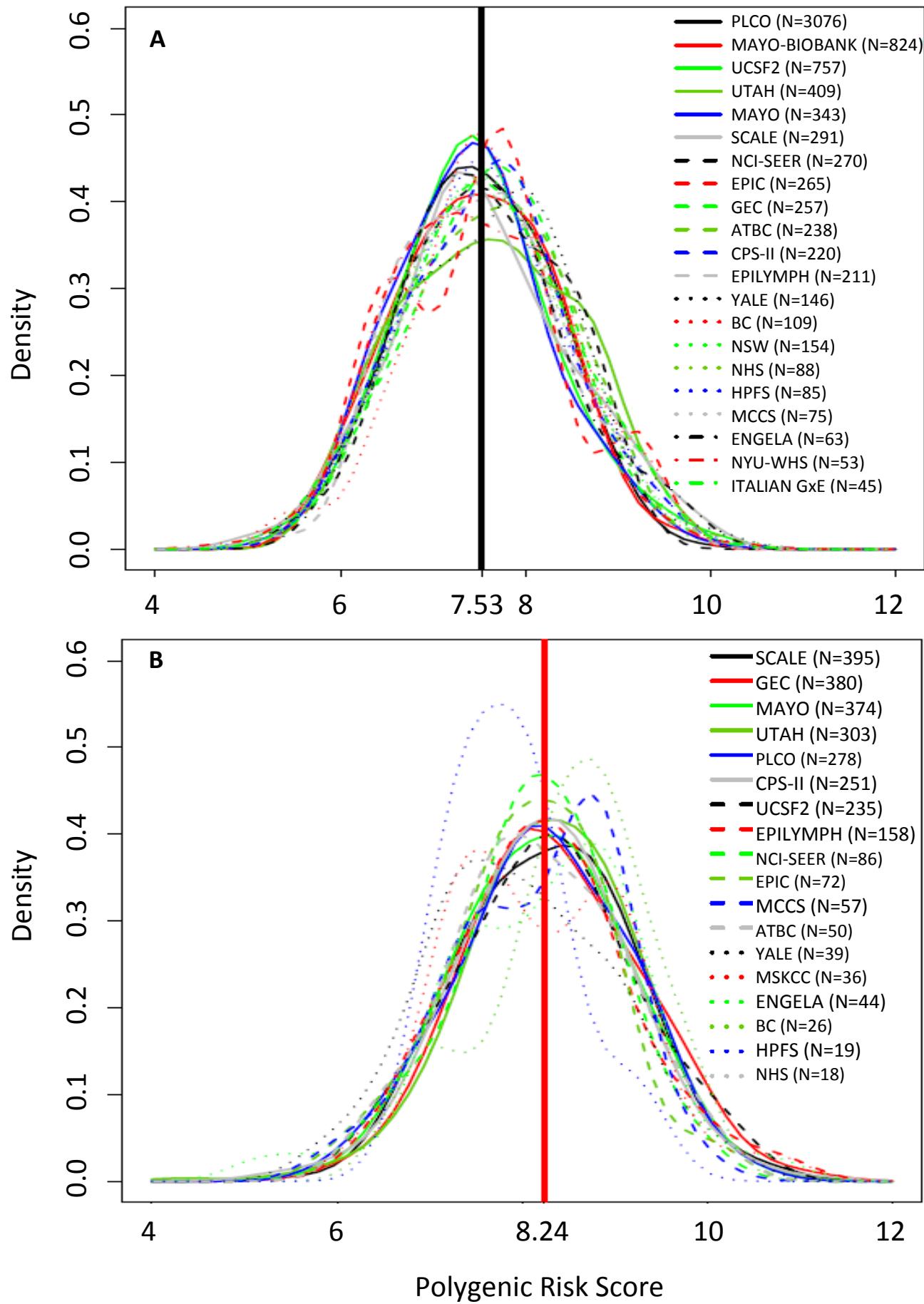
Supplemental Figure 1: Polygenic risk score distribution by overall and subset of NHL GWAS case-controls and independent Mayo Clinic controls



Histograms of polygenic risk scores (x-axis) and density (y-axis) by all NHL GWAS: CLL (solid red line) and controls (solid black line), a subset of 8 InterLymph studies with both GWAS and exposure data: CLL (dashed red line) and controls (dashed black line), and independent Mayo controls (dotted black line). The vertical lines indicate the median for the corresponding polygenic risk score distribution.

InterLymph=International Lymphoma Epidemiology Consortium; Mayo=Mayo Clinic; CLL=chronic lymphocytic leukemia; NHL=non-Hodgkin lymphoma; GWAS=genome-wide association studies

Supplemental Figure 2: Polygenic risk score distribution of CLL and controls by NHL GWAS studies with N>15 per study

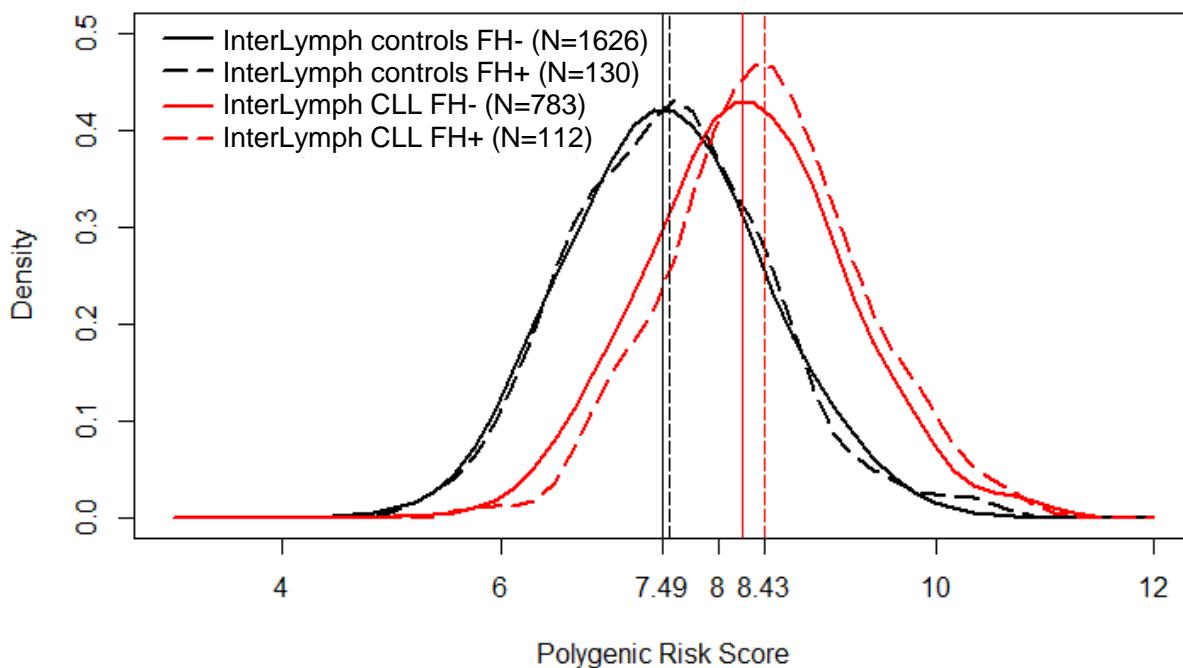


Histograms of polygenic risk scores (x-axis) and density (y-axis) by NHL GWAS studies with N>15 individuals per study;
(A) controls; (B) CLL.

The vertical lines indicate the overall median for the corresponding polygenic risk score distribution, black for controls and red for CLL.

InterLymph=International Lymphoma Epidemiology Consortium; CLL=chronic lymphocytic leukemia; NHL=non-Hodgkin lymphoma; GWAS=genome-wide association studies

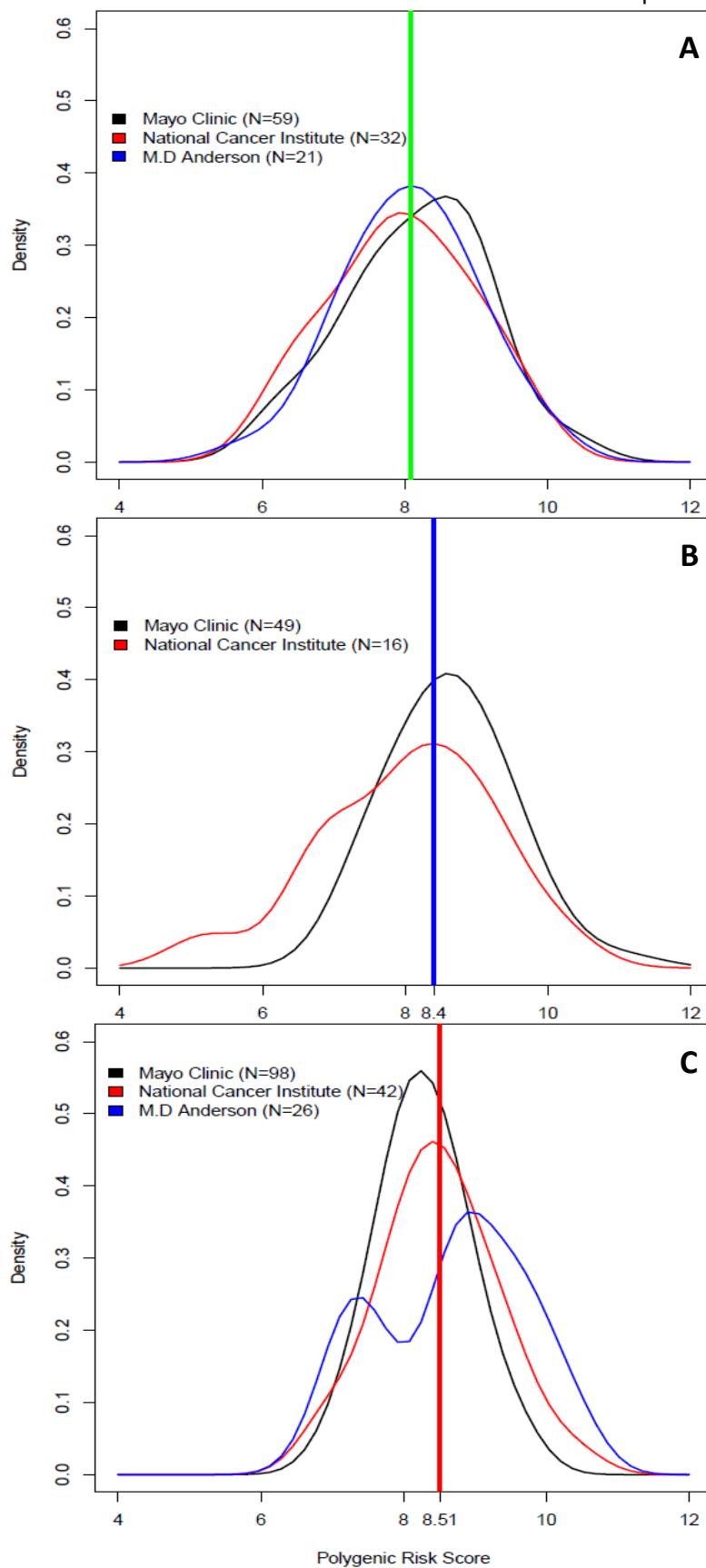
Supplemental Figure 3: Polygenic risk score distribution by family history status among subset of 8 InterLymph case-control studies



Histograms of polygenic risk scores (x-axis) and density (y-axis) by controls FH- (solid black line) and controls FH+ (dashed black line), CLL FH- (solid red line) and CLL FH+ (dashed red line). The vertical lines indicate the median for the corresponding polygenic risk score distribution.

InterLymph=International Lymphoma Epidemiology Consortium; CLL=chronic lymphocytic leukemia; FH-=family history negative; FH+=family history positive

Supplemental Figure 4: Polygenic risk score distribution of controls, MBL, CLLs of validation samples from GEC consortium for those recruitment sites with >15 individuals recruited per site

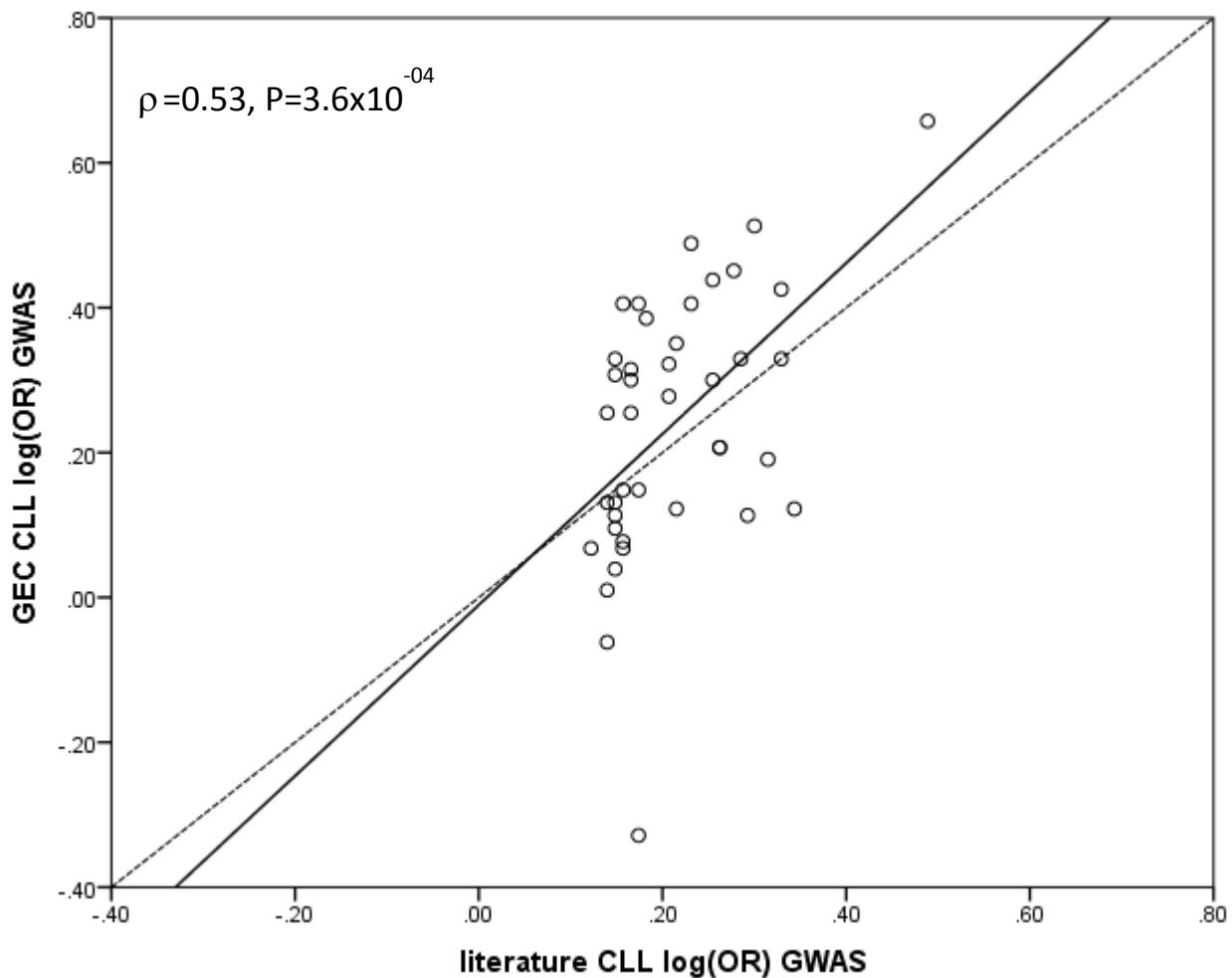


Histograms of polygenic risk scores (x-axis) and density (y-axis) by GEC recruitment sites with N>15 individuals per site;
(A) controls; (B) MBL; (C) CLL.

The vertical lines indicate the overall median for the corresponding polygenic risk score distribution, green for controls,
blue for MBL and red for CLL.

GEC=Genetic Epidemiology of CLL Consortium; CLL=chronic lymphocytic leukemia; MBL=monoclonal B-cell
lymphocytosis;

Supplemental Figure 5: Association between the log(OR) of the 41 SNPs associated with CLL from the literature and the log(OR) of GEC CLL vs Mayo controls



Association between the log(OR) of the 41 SNPs associated with CLL from the literature and the log(OR) of GEC CLL (N=201) vs Mayo controls (N=1267) with Pearson correlation (ρ). Dashed line represents perfect concordance; solid line represents the fitted line.

GEC=Genetic Epidemiology of CLL Consortium; OR=Odds Ratio; CLL= Chronic Lymphocytic Leukemia; SNP= Single Nucleotide Polymorphism; GWAS=Genome Wide Association Study

Supplemental Table 1: Demographic characteristics for all CLL cases and controls from NHL studies in the NHL GWAS initiative

Study name	Study Abbreviation	Study Location	Study Design	CLL N=2849		Control N=7983		Male CLL cases		Male controls		Age CLL cases	Age controls
				N	column %	N	column %	N	row %	N	row %	Median (range)	Median (range)
Scandinavian Lymphoma Etiology Study Genetic Epidemiology of CLL (GEC) Consortium	SCALE	Sweden, Denmark	Population-based case-control study	395	13.9%	291	3.6%	262	66.3%	168	57.7%	63 (30-74)	64 (20-75)
Iowa-Mayo SPOR-E Molecular Epidemiology Resource and Mayo Clinic Case-Control Study of NHL and CLL	GEC	USA	Family study	380	13.3%	257	3.2%	245	64.5%	163	63.4%	62 (27-90)	64 (27-87)
Utah Chronic Lymphocytic Leukemia Study	MAYO	USA	Clinic-based case registry and Clinic-based case-control study	374	13.1%	343	4.3%	269	71.9%	210	61.2%	63 (32-91)	63 (19-93)
Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial American Cancer Society Cancer Prevention Study II Nutrition Cohort	UTAH	USA	Mixed: clinic and population-based cases and controls	303	10.6%	409	5.1%	178	59.7%	223	55.8%	64 (32-84)	65 (27-91)
	PLCO	USA	Nested case-control	278	9.8%	3076	38.5%	157	56.5%	2943	95.7%	70 (57-86)	70 (55-87)
	CPS-II	USA	Nested case-control	251	8.8%	220	2.8%	132	52.6%	109	49.5%	71 (57-85)	68 (54-87)

Molecular Epidemiology of non-Hodgkin lymphoma	UCSF2	USA	Population-based case-control study	235	8.2%	757	9.5%	151	64.3%	437	57.7%	64 (30-84)	62 (20-84)
Epilymph case-control study in six European countries	EPILYMPH	Europe	Multicenter case-control study, hospital-based and population-based	158	5.5%	211	2.6%	104	65.8%	114	54.0%	64 (30-87)	62 (19-85)
National Cancer Institute Surveillance, Epidemiology, and End Results Interdisciplinary Case-Control Study of Non-Hodgkin's Lymphoma	NCI-SEER	USA	Population-based case-control study	86	3.0%	270	3.4%	51	59.3%	146	54.1%	62 (38-74)	59 (21-74)
European Prospective Investigation into Cancer, Chronic Diseases, Nutrition and Lifestyles The Melbourne Collaborative Cohort Study Alpha-Tocopherol, Beta Carotene Lung Cancer Prevention Study Environmental and genetic	EPIC	multiple European countries	Nested case-control	72	2.5%	265	3.3%	39	54.2%	120	45.3%	64 (41-83)	63 (44-84)
	MCCS	Australia	Nested case-control	57	2.0%	75	0.9%	34	59.6%	39	52.0%	65 (35-84)	71 (58-84)
	ATBC	Finland	Nested case-control	50	1.8%	238	3.0%	50	100.0%	238	100.0%	72 (60-89)	68 (50-86)
	ENGELA	France	Hospital-based case-	44	1.5%	63	0.8%	29	65.9%	41	65.1%	62 (37-74)	57 (20-75)

risks factors study in adult lymphoma	control study												
	YALE	USA	Population-based case-control study	39	1.4%	146	1.8%	0	0.0%	0	0.0%	68 (42-84)	62 (26-85)
Memorial-Sloan-Kettering Lymphoproliferative disorders Study	MSKCC	USA	Hospital-based case-study and NYCP controls	36	1.3%	4	0.1%	21	58.3%	0	0.0%	63 (36-80)	39 (31-56)
British Columbia Non-Hodgkin Lymphoma Study	BC	Canada	Population-based case-control study	26	0.9%	109	1.4%	20	76.9%	61	56.0%	65 (50-80)	62 (24-80)
Health Professionals Follow-up Study	HPFS	USA	Nested case-control	19	0.7%	85	1.1%	19	100.0%	85	100.0%	71 (54-85)	71 (50-85)
Nurses' Health Study	NHS	USA	Nested case-control	18	0.6%	88	1.1%	0	0.0%	0	0.0%	65 (49-73)	64 (48-77)
NSW non-Hodgkin lymphoma study	NSW	Australia	Population-based case-control study	13	0.5%	154	1.9%	8	61.5%	93	60.4%	64 (42-73)	58 (22-73)
New York University Women's Health Study Multicenter Italian study on gene-environment interactions in lymphoma etiology: translational	NYU-WHS	USA	Nested case-control	10	0.4%	53	0.7%	0	0.0%	0	0.0%	71 (57-80)	79 (56-89)
ITALIAN GxE	Italy	Population-based case-control study	5	0.2%	45	0.6%	4	80.0%	28	62.2%	68 (61-74)	54 (31-76)	

aspects												
Mayo Clinic												
Biobank	MAYO-											
Controls	BIOBANK	USA	Hospital-based	0	0	824	10.3%	0	0	411	49.9%	NA
												66 (35-85)

CLL=chronic lymphocytic leukemia; NHL=non-Hodgkin lymphoma;
GWAS=Genome Wide Association Studies

Supplemental Table 2: List of 41 SNPs associated with CLL risk from a fine mapping study and the association with CLL/MBL/Control risk from the GEC Consortium compared to Mayo controls

Locus	Nearest Gene(s)	Previously Published	Lead SNP in	LD	Position	Risk	Results from a published study (effect sizes used for the PRS calculations)		Association between GEC CLL (n=201) vs Mayo controls (n=1267)		Association between GEC MBL (n=95) vs Mayo controls (n=1267)	
		SNP with updated P and OR	Published fine mapping GWAS	(r ²)	(hg19, bp)	Allele	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
1p36.11	MDS2		rs34676223		23943735	C	1.19 (1.14-1.25)	5.04E-13	1.16 (0.91-1.48)	0.23	1.29 (0.91-1.83)	0.15
1q42.13	RHOU		rs41271473		228880296	G	1.19 (1.13-1.26)	1.06E-10	0.72 (0.57-0.92)	0.009	0.98 (0.68-1.41)	0.90
2p22.2	QPCT, PRKD3		rs888096		37,603,801	A	1.15 (1.09-1.21)	5.20E-08	1.14 (0.91-1.41)	0.26	1.10 (0.81-1.50)	0.54
2q13	ACOXL, BCL2L11	rs1002015			111,616,619	C	1.30 (1.23-1.37)	2.23E-23	1.23 (0.98-1.53)	0.07	1.55 (1.12-2.15)	0.008
		rs58055674			111,831,793	C	1.41 (1.32-1.5)	2.02E-27	1.13 (0.87-1.46)	0.35	1.32 (0.94-1.86)	0.11
		rs6708784			111,927,379	G	1.30 (1.24-1.37)	2.67E-25	1.23 (0.99-1.53)	0.05	1.14 (0.85-1.54)	0.39
2q33.1	CASP10/CASP8		rs7558911		202,023,949	A	1.18 (1.12-1.24)	5.05E-11	1.29 (1.04-1.61)	0.02	1.11 (0.82-1.49)	0.52
2q37.1	SP110, SP140		rs34004493		231,154,012	G	1.39 (1.31-1.47)	3.67E-32	1.53 (1.21-1.92)	3.00E-04	1.44 (1.05-1.98)	0.03
2q37.3	FARP2	rs757978		0.64	242,371,101	T	1.29 (1.2-1.39)	5.80E-11	1.55 (1.14-2.11)	0.005	1.45 (0.93-2.25)	0.10
2q37.3	FARP2		rs3755397^		242,294,913	G	1.32 (1.22-1.43)	9.48E-12				
3p24.1	EOMES	rs9880772			27,777,779	A	1.16 (1.11-1.22)	1.91E-09	1.04 (0.84-1.29)	0.72	1.02 (0.76-1.39)	0.88
3q26.2	MYNN, TERC		rs1317082		169,497,585	A	1.19 (1.12-1.26)	5.77E-09	1.50 (1.14-1.96)	0.003	1.24 (0.86-1.77)	0.25
4q24	BANK1		rs13107612*		102739980	C	1.17 (1.11-1.22)	1.37E-10	1.16 (0.91-1.47)	0.24	1.25 (0.89-1.76)	0.20
4q25	LEF1		rs7690934		109,025,865	C	1.16 (1.11-1.22)	6.08E-09	1.36 (1.08-1.70)	0.008	1.20 (0.88-1.65)	0.24
4q35.1	LOC728175		rs57214277		185254772	T	1.13 (1.08-1.18)	3.69E-08	1.07 (0.87-1.33)	0.52	0.99 (0.73-1.34)	0.96
5p15.33	TERT		rs7705526		1,285,974	A	1.18 (1.12-1.25)	5.90E-10	1.35 (1.08-1.69)	0.008	1.38 (1.02-1.87)	0.04
6p25.3	IRF4		rs9392504		412,802	A	1.33 (1.26-1.4)	9.81E-29	1.39 (1.12-1.73)	0.003	1.52 (1.12-2.07)	0.01
6p21.32	HLA		rs9271176		32,578,127	G	1.29 (1.22-1.36)	3.16E-20	1.35 (1.06-1.73)	0.02	1.20 (0.86-1.66)	0.29
6p21.31	BAK1		rs210143		33,546,930	C	1.26 (1.19-1.33)	5.77E-16	1.63 (1.25-2.12)	3.15E-04	1.07 (0.77-1.48)	0.70
6p21.31	C6orf106		rs3800461		34616322	C	1.20 (1.13-1.28)	1.97E-08	1.47 (1.09-1.98)	0.01	1.16 (0.74-1.82)	0.52
6q25.2	IPCEF1		rs4869818		154,471,225	G	1.15 (1.09-1.21)	4.11E-08	0.94 (0.76-1.16)	0.57	1.02 (0.76-1.37)	0.90
7q31.33	POT1		rs2267708		124,392,512	T	1.16 (1.1-1.22)	8.55E-09	1.12 (0.91-1.39)	0.28	1.33 (0.99-1.79)	0.06
8q22.3	ODF1		rs2511713		103,577,865	G	1.17 (1.1-1.23)	6.04E-08	1.07 (0.84-1.35)	0.60	1.03 (0.74-1.44)	0.84
8q24.21	POU5F1B		rs2466029		128,200,971	G	1.23 (1.17-1.3)	7.47E-16	1.32 (1.05-1.64)	0.02	1.12 (0.82-1.54)	0.47
9p21.3	CDKN2B-AS1	rs1679013			22,206,987	C	1.16 (1.1-1.22)	2.17E-08	1.10 (0.89-1.36)	0.40	1.17 (0.87-1.58)	0.30
10q23.31	ACTA, FAS		rs6586163		90,752,018	A	1.23 (1.17-1.29)	1.14E-15	1.38 (1.11-1.72)	0.004	1.27 (0.94-1.71)	0.13

11p15.5	<i>C11orf21, TSPAN32</i>		rs2651823	2,321,650	A	1.18 (1.13-1.25)	5.24E-11	1.37 (1.11-1.70)	0.004	1.16 (0.86-1.56)	0.33
11q23.2	TMPRSS5		rs61904987	113517203	T	1.24 (1.16-1.32)	2.46E-11	1.13 (0.82-1.54)	0.46	1.00 (0.64-1.58)	0.98
11q24.1	<i>SCN3B, GRAMD1B</i>		rs35923643	123,355,391	G	1.63 (1.53-1.72)	4.26E-58	1.93 (1.53-2.44)	3.75E-08	1.73 (1.26-2.39)	0.001
12q24.13	OAS3		rs6489882	113,381,376	G	1.16 (1.1-1.22)	4.76E-08	1.39 (1.12-1.72)	0.003	1.24 (0.91-1.68)	0.17
15q15.1	<i>BMF, BUB1B</i>	rs8024033		40,403,657	C	1.26 (1.2-1.32)	7.13E-19	1.50 (1.20-1.87)	3.05E-04	1.33 (0.98-1.80)	0.07
15q21.3	<i>RFX7, NEDD4</i>		rs142215530	56,777,691	G	1.39 (1.29-1.5)	2.46E-18	1.39 (1.02-1.89)	0.04	0.92 (0.57-1.49)	0.74
15q23	<i>RPLP1</i>		rs11637565	70,020,525	G	1.35 (1.28-1.42)	1.96E-31	1.67 (1.35-2.08)	3.00E-06	1.50 (1.11-2.02)	0.008
16q24.1	<i>IRF8</i>		rs305065	85,973,866	C	1.16 (1.1-1.22)	7.57E-08	1.14 (0.91-1.42)	0.26	1.11 (0.82-1.52)	0.50
			rs391855	85,928,621	A	1.34 (1.27-1.41)	1.25E-28	1.12 (0.90-1.40)	0.32	1.75 (1.25-2.44)	0.001
18q21.1	CXXC1		rs1036935	47843534	A	1.15 (1.10-1.21)	3.27E-08	1.29 (1.02-1.64)	0.04	1.47 (1.07-2.04)	0.02
18q21.32	<i>PMAIP1</i>	rs4368253		57,622,287	C	1.17 (1.11-1.24)	1.26E-08	1.08 (0.86-1.37)	0.51	0.92 (0.70-1.27)	0.62
18q21.33	<i>BCL2</i>		rs77551289	60,788,745	A	1.37 (1.25-1.5)	1.83E-11	1.21 (0.80-1.81)	0.37	1.38 (0.76-2.52)	0.29
			rs4987852	60,793,921	C	1.32 (1.2-1.44)	4.66E-09	1.57 (1.07-2.28)	0.02	2.33 (1.47-3.67)	2.93E-04
19p13.3	ZBTB7A		rs7254272	4069119	A	1.17 (1.10-1.73)	4.67E-08	1.50 (1.16-1.94)	0.002	1.73 (1.22-2.46)	0.002
19q13.3	<i>PRKD2, STRN4</i>		rs874460	47,176,752	C	1.24 (1.15-1.34)	3.37E-08	1.42 (0.99-2.04)	0.06	1.18 (0.73-1.90)	0.49
22q13.33	NCAPH2		rs140522	50971266	T	1.15 (1.10-1.20)	2.70E-09	1.01 (0.80-1.26)	0.96	1.07 (0.78-1.47)	0.66

^aNot imputed

*Proxy for rs71597109

GEC=Genetic Epidemiology of CLL Consortium; CLL=chronic lymphocytic leukemia; MBL=monoclonal B-cell lymphocytosis;

OR=Odds Ratio; CI=Confidence Interval; LD=Linkage Disequilibrium; ^aNot imputed; *Proxy for rs71597109

Supplemental Table 3: Exposures and genetic factors from InterLymph by case-control status and the association with CLL risk

Characteristics	Category	Controls N=2459		Cases N=1499		Basic Model*			Multivariable Model**			Multivariable Model***			Multivariable Model**** (overall)			
		N	%	N	%	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	
PRS	Median	7.5		8.25		2.49	2.28-2.80	<0.0001							2.33	1.97-2.76	<0.0001	
Any FH PRS	Yes	130	7.4%	112	12.5%	2.04	1.53-2.73	<0.0001	1.82	1.33-2.49	<0.0001					2.02	1.27-3.22	0.003
	Missing	703		604					2.53	2.27-2.83	<0.0001					Pinter=0.21		
Atopy PRS	Yes	937	39.2%	382	31.1%	0.75	0.64-0.88	<0.0001	0.74	0.63-0.88	<0.0001	0.93	0.76-1.13	0.45		0.92	0.67-1.28	0.63
	FH								2.46	2.25-2.70	<0.0001	2.53	2.27-2.83	<0.0001				
Asthma PRS	Yes	228	11.3%	109	9.8%	0.98	0.76-1.27	0.89	0.96	0.73-1.26	0.76	1.14	0.81-1.60	0.47				
	FH								2.58	2.33-2.85	<0.0001	2.70	2.39-3.06	<0.0001				
Eczema PRS	Yes	194	9.8%	99	9.7%	0.98	0.74-1.30	0.89	0.99	0.73-1.34	0.94	1.04	0.76-1.44	0.81				
	FH								2.59	2.32-2.88	<0.0001	2.59	2.31-2.91	<0.0001				
Hay fever PRS	Yes	525	30.0%	179	20.2%	1.1	0.88-1.37	0.4	1.1	0.87-1.40	0.45	1.13	0.88-1.46	0.35				
	FH								2.53	2.26-2.83	<0.0001	2.55	2.26-2.88	<0.0001				
Allergies PRS	Yes	672	33.6%	266	26.4%	0.94	0.78-1.14	0.42	0.93	0.76-1.15	0.52	0.98	0.79-1.23	0.89				
	FH								2.48	2.23-2.76	<0.0001	2.49	2.22-2.79	<0.0001				
											Pinter=0.73	1.96	1.41-2.71	<0.0001				

	Missing	458	493															
Food PRS FH	Yes	173	9.6%	68	7.3%	1.17	0.84-1.63	0.35	1.21	0.84-1.74	0.3	1.23	0.84-1.82	0.29				
									2.46	2.21-2.74	<0.0001	2.47	2.20-2.77	<0.0001				
	Missing	653		569						Pinter=0.77	1.86	1.32-2.62	<0.0001					
Ever living/working on a farm PRS FH	Yes	582	41.4%	294	50.8%	1.11	0.89-1.39	0.34	1.06	0.84-1.34	0.65	1.03	0.81-1.31	0.83	0.92	0.67-1.26	0.61	
									2.46	2.17-2.79	<0.0001	2.45	2.15-2.78	<0.0001				
	Missing	1052		920						Pinter=0.85	1.87	1.31-2.65	<0.0001					
Recreational sun exposure PRS FH	Q1 (low)	238	25.0%	246	41.1%	Ref			Ref			Ref						
	Q2	209	22.0%	185	30.9%	1.14	0.85-1.52	0.39	1.07	0.78-1.46	0.69	1.25	0.87-1.80	0.23				
	Q3	261	27.4%	79	13.2%	0.87	0.55-1.39	0.57	0.79	0.48-1.30	0.35	0.91	0.54-1.52	0.71				
	Q4 (High)	244	25.6%	89	14.9%	1.02	0.64-1.62	0.94	0.89	0.54-1.46	0.89	1.12	0.66-1.89	0.67				
PRS FH	Continuous				1.01	0.87-1.18	0.86	0.98	0.94-1.03	0.47	1.00	0.96-1.05	0.99					
								2.38	2.07-2.73	<0.0001	2.39	2.04-2.79	<0.0001					
	Missing	1507		900						Pinter=0.93	2.02	1.21-3.38	0.007					
Total sun exposure PRS FH	Q1 (low)	334	33.6%	162	38.5%	Ref			Ref			Ref						
	Q2	312	31.4%	137	32.5%	0.91	0.68-1.23	0.55	0.99	0.73-1.36	0.97	1.02	0.74-1.40	0.93				
	Q3	235	23.6%	77	18.3%	0.67	0.46-0.98	0.04	0.7	0.47-1.05	0.09	0.71	0.47-1.09	0.11				
	Q4 (High)	113	11.4%	45	10.7%	0.66	0.37-1.16	0.15	0.69	0.37-1.27	0.23	0.78	0.41-1.48	0.45				
PRS FH	Continuous				0.85			0.98	0.96-0.99	0.04	0.98	0.96-1.01	0.08	0.98	0.96-1.00	0.09		
								2.39	2.07-2.77	<0.0001	2.39	2.05-2.77	<0.0001					
	Missing	1465		1078						Pinter=0.36	1.85	1.22-2.81	0.004					

Height (10 cm)	Mean (SD)	17.2	(0.98)	17.4	(0.95)	1.2	1.06-1.36	0.004	1.19	1.04-1.36	0.01	1.18	1.03-1.36	0.02	1.09	0.88-1.36	0.42
PRS									2.52	2.27-2.80	<0.0001	2.51	2.24-2.80	<0.0001			
FH										Pinter=0.17	1.82	1.33-2.50	<0.0001				

InterLymph=International Lymphoma Epidemiology Consortium; CLL=chronic lymphocytic leukemia ; OR=Odds Ratio; CI=Confidence Interval;
 PRS=Polygenic Risk Score; FH=Family History; *Adjusted for age, sex, SES and study; **Adjusted for age, sex, SES, study and PRS; ***Adjusted for age, sex, socioeconomic status and study, PRS and FH; ****Adjusted for age, sex, socioeconomic status, study, PRS, FH, atopy, farming, total sun exposure, and height